Factors modifying stress from adverse effects of immunosuppressive medication in kidney transplant recipients

Rosenberger, J.; Geckova, A.M.; van Dijk, J.P.; Roland, R.; Groothoff, J.W.

Published in:
Clinical Transplantation

DOI:
10.1111/j.1399-0012.2004.00300.x

Publication date:
2005

Clin Transplant 2005: 19: 70–76 DOI: 10.1111/j.1399-0012.2004.00300.x

Clinical Transplantation

Factors modifying stress from adverse effects of immunosuppressive medication in kidney transplant recipients

Rosenberger J, Geckova AM, van Dijk JP, Roland R, van den Heuvel WJA, Groothoff JW. Factors modifying stress from adverse effects of immunosuppressive medication in kidney transplant recipients. Clin Transplant 2005: 19: 70–76. © Blackwell Munksgaard, 2004

Abstract: Introduction: The adverse effects of immunosuppression appear in the majority of patients with a negative impact on morbidity, mortality and quality of life. The group of adverse symptoms manifested as changes in appearance, mood and energy are often more stressful than serious metabolic changes because of their direct negative influence on patients' well-being. The aim of this study is to explore the adverse symptoms of immunosuppressive medication which are the most stressful for transplanted patients, and which are the modifying factors.

Patients and methods: A total of 157 adult kidney transplant recipients from two transplant centres in Slovakia with a functioning graft transplanted <7 yr ago were examined. Patients participated in an interview focusing on stress from adverse effects, and their education and social support. Medical records were searched for information about immunosuppression protocols, dialysis treatment before transplantation, type of received organ and period after transplantation. The effect of the selected variables on the total score for stress from adverse effects was tested using ANOVA. The effect of the selected factors on stress from each single adverse effect was explored using *t*-test and ANOVA.

Results: The most stressful symptoms were pain, weakness, weight gain, facial changes, depression and anxiety. The mean value of the total score for stress from adverse effects was 8.03 ± 6.53 (minimum 0, maximum 30, range: 0–64), indicating low stress. Women and patients with lower education significantly more often felt the adverse effects of immunosuppression as stressful ($p < 0.001$ and $p < 0.05$, respectively). Age, social support, dialysis modality before transplantation, time from transplantation and type of immunosuppressive treatment did not affect the total score for stress from adverse effects. However, variables that were not significant in the overall score reached significance in some symptoms.

Conclusions: Women and patients with lower education significantly more often felt the adverse effects of immunosuppression as stressful; in a more detailed analysis the use of new drugs was connected with less stress in some symptoms. The use of these drugs can improve life quality for transplant recipients, decrease non-compliance, and thus prevent graft loss.

Jaroslav Rosenberger[a], Andrea Madarasova Geckova[b], Jitse P van Dijk[c], Robert Roland[a], Wim JA van den Heuvel[d] and Johan W Groothoff[c]

[a] Transplantation Department, University Hospital, Košice, Slovak Republic, [b] Institute of Social Sciences, Faculty of Sciences, University of P.J. Safarik, Košice, Slovak Republic, [c] Department of Social Medicine, University of Groningen, Groningen, The Netherlands and [d] Institute for Rehabilitation Research, Hoensbroek and University of Maastricht, Maastricht, The Netherlands

Key words: adverse effects – immunosuppression – kidney transplantation – quality of life – stress

Corresponding author: Jaroslav Rosenberger MD, Transplantation Department, University Hospital, Tr. SNP 1, 040 66 Košice, Slovak Republic.
Tel.: +421 903 193089; fax: +421 55 6432661;
e-mail: rosenberger_jaro@hotmail.com

Accepted for publication 3 September 2004

Successful kidney transplantation requires effective immunosuppression. However, immunosuppressive drugs are well-known for their wide range of adverse effects; this puts them into one of the top positions in the rankings of various stressors (1–3).

Among the most significant adverse effects are infections, because of their graft and life-threatening

potential (4). New immunosuppressive drugs in particular are very effective in preventing acute and chronic kidney damage, but they also increase the potential for various infections (5). Oncological adverse effects are very menacing, and the risk of acquiring cancer is three- to five-fold higher in transplanted patients when compared with the standard population (6, 7). The most common adverse effects are hypertension and metabolic changes (e.g. diabetes, hyperuricaemia, hypercholesterolaemia), and their importance lies in their negative influence on long-term cardiovascular morbidity and mortality (8, 9).

Besides these well-known effects another group of adverse symptoms causes distress to transplanted patients. These emerge as the results of the complex mechanism of immunosuppressive treatment and they become manifest as changes of appearance, mood and energy (10–12). For patients, these symptoms are often more stressful than serious metabolic changes because of the direct negative influence on their well-being (12, 13). Deterioration of well-being may even cause non-compliant behaviour (14, 15), which is one of the leading causes of late acute rejection and graft loss (16–18).

Traditionally, a number of side-effects are linked to steroids. They are responsible for weight gain, weakness, negative psychological symptoms, oedemas and skin changes (19, 20). Increased growth of gum and hair is usually connected with calcineurin inhibitors.

The adverse effects of immunosuppression appear in the majority of patients and they have a negative impact on morbidity and mortality as well as on quality of life. This makes follow-up necessary (21).

The aim of this study was to explore which non-infectious, non-oncological adverse symptoms of immunosuppressive medication are the most stressful for a transplanted patient. It also focuses on the contribution of various socio-demographic, medical factors and social support to the development of stress from these adverse effects. Finally, the study explores the role of these factors affecting stress from each separate adverse effect.

Patients and methods

Patients

Data collection took place from September 2002 to September 2003 in two transplant centres in Slovakia (Košice and Bratislava). Adult kidney transplant recipients with a functioning graft transplanted < 7 yr ago were informed about the study by their nephrologist. Of 167 informed patients, 157 agreed to participate. The only exclusion criterion was the inability to answer questions during the interview because of severe dementia or mental retardation. All patients signed an informed consent before the interview. The study was approved by the local ethical committee.

Interview

Each patient participated in an interview with a trained interviewer focusing on the stress from adverse effects of immunosuppression. Based on a literature search (19, 20, 22, 23) and the results of a small pilot study, 16 various adverse symptoms of immunosuppression were identified. Stress from each of these adverse effects of immunosuppression was measured with a 5-point scale (0, no stress; 1, low stress; 2, moderate stress; 3, high stress; 4, very high stress). For each patient, a total score of all adverse effects was calculated as the sum of scores in all items (possible range: 0–64).

Education was categorized as elementary, secondary or university. Satisfaction with social support was also measured using a 5-point scale (1, excellent; 2, good; 3, fair; 4, poor; 5, bad). However, after preliminary results this variable was trichotomized by merging three last categories (1, excellent; 2, good; 3, bad).

Medical records

Patient medical records were searched for information about their immunosuppressive regimen, dialysis treatment before transplantation (haemodialysis, peritoneal dialysis or both methods), type of received organ (cadaveric, living) and the moment of transplantation.

Statistics

Statistical analysis was performed using SPSS 10.1.0 (SPSS Inc., Chicago, IL, USA). The effect of selected socio-demographic variables (age, gender, education), social support, dialysis modality before transplantation, time from transplantation and immunosuppressive regimen on the total score for stress from adverse effects was tested using ANOVA. Two models were explored: one model including the main effects and all two-way interactions and one without interactions. The effect of selected factors on stress from each single adverse effect was explored using a *t*-test for dichotomous (age, gender, immunosuppression treatment) and one-way ANOVA for trichotomous (education, social support, time from transplantation) variables.

Post-hoc tests were performed for variables that were found to be significant in ANOVA.

Results

The sample consisted mainly of middle-aged cadaveric kidney recipients with secondary education and haemodialysis treatment before transplantation. The majority of patients declared their social support as excellent or good, and the mean score for social support was 1.66 ± 0.8 (range: 1–3), indicating a supportive environment. Nearly all patients had their immunosuppressive protocol based on cyclosporin (CsA), and the predominant regimen consisted of prednison (P), CsA and mycofenolate mofetil (MMF). According to their immunosuppressive regimens patients were considered to be steroid-treated (75.8%), CsA-treated (95.4%), mycofenolate-treated (59.5%), azathioprin (Aza)-treated (17.6%) and tacrolimus (Tac)-treated (4.6%). A more detailed description of the patient sample is shown in Table 1.

Results of stress from each single adverse effect are presented in Table 2 in descending order according to stressfulness. The most stressful symptoms were pain, malaise, muscle weakness and major physical cosmetic changes such as weight gain and facial changes, followed by psychological symptoms (depression and anxiety). The total score for stress from all items varied between 0 and 30 (possible range: 0–64), and the mean value for the whole sample was 8.03 ± 6.53, indicating low mean stress.

The effects of gender, age, education, social support, modality of dialysis before transplantation, immunosuppression protocol and time from transplantation on stress from adverse effects of immunosuppression were analysed (Table 3). None of the explored two-way interactions were significant, so only the model including main effect without interactions is described. Women compared with men ($p < 0.001$), and patients with lower education compared to those with university education ($p < 0.05$), more often felt the adverse effects of immunosuppression as stressful. Age, social support, dialysis modality before transplantation, time from transplantation and modality of immunosuppressive treatment did not affect the total score for stress from adverse effects.

On the contrary, the main effect of the selected variables on the score for stress is not visible in each symptom. In addition, variables that were not significant in the overall score (age, social support, modality of dialysis, time from transplantation) reached significance in some symptoms. These results are presented in Table 4. Women felt pain,

Table 1. Basic description of patient sample and treatment characteristics (n = 157)

Variable	N	Percentage/mean and SD (range)
Gender		
Male	94	59.9
Female	63	40.1
Age (yr)		47.7 ± 11.7 (18.3–74)
≤ 50	90	58.1
>50	65	41.9
Education		
Elementary	28	18.7
Secondary	107	71.3
University	15	10.0
Social support		1.66 ± 0.8 (1–3)
Excellent	74	50.7
Good	53	36.3
Bad	19	13.0
Organ donor		
Living donor	4	2.6
Cadaveric donor	151	97.4
Dialysis before transplantation		
Haemodialysis	119	79.9
Peritoneal dialysis	19	12.8
Both	11	7.3
Time from transplantation		37.7 ± 27.3 months (3–144)
≤ 3 months	24	15.5
4–36 months	56	36.1
>36 months	75	48.4
Immunosuppressive regimen		
CsA	11	7.1
P + CsA	24	15.6
CsA + Aza	6	3.9
CsA + MMF	20	13.0
P + CsA + Aza	21	13.6
P + CsA + MMF	65	42.2
P + Tac + MMF	7	4.5

P, prednison; CsA, cyclosporin A; Aza, azathioprin; MMF, mycofenolate mofetil; Tac, tacrolimus.

Table 2. Scores for stress from adverse effects of immunosuppression

Symptom	Mean ± SD (range)
Pain	0.90 ± 1.05
Malaise	0.87 ± 1.01
Muscle weakness	0.79 ± 0.96
Weight gain	0.77 ± 1.00
Facial changes	0.66 ± 0.94
Depression	0.58 ± 0.94
Fear, anxiety	0.58 ± 0.95
Sleep disorders	0.49 ± 0.84
Gingival hyperplasia	0.43 ± 0.89
Skin lesions	0.38 ± 0.83
Leg oedemas	0.38 ± 0.80
Hair loss	0.34 ± 0.82
Sexual dysfunction	0.33 ± 0.81
Facial oedemas	0.22 ± 0.52
Diarrhoea	0.18 ± 0.56
Fragile skin	0.12 ± 0.47
Mean total score for stress from all items	8.03 ± 6.53 (0–30)

Table 3. Effects of selected factors on total score for stress from adverse effects of immunosuppression

Factor	Mean ± SD	p-Value
Gender		
Male	6.28 ± 5.51	0.000**
Female	10.46 ± 7.00	
Age (yr)		
≤ 50	8.06 ± 6.62	0.540
>50	7.62 ± 6.22	
Education		
Elementary	9.96 ± 8.16	0.027*
Secondary	7.89 ± 5.90	
University	3.57 ± 3.92	
Social support		
Excellent	7.51 ± 6.15	0.559
Good	8.31 ± 6.42	
Bad	8.06 ± 7.77	
Dialysis before transplantation		
Haemodialysis	8.00 ± 6.47	0.671
Peritoneal dialysis	7.61 ± 6.48	
Both modalities	7.00 ± 6.48	
Time from transplantation (month)		
≤ 3	7.38 ± 5.27	0.555
4–36	6.92 ± 5.87	
>36	8.71 ± 7.06	
Immunosuppression protocol		
CsA	7.60 ± 6.59	0.612
P, CsA	9.61 ± 8.05	
CsA, Aza	5.33 ± 4.41	
CsA, MMF	6.88 ± 5.35	
P, CsA, Aza	9.90 ± 7.03	
P, CsA, MMF	7.07 ± 5.99	
P, Tac, MMF	8.14 ± 5.58	

P, prednison; CsA, cyclosporin A; Aza, azathioprin; MMF, mycofenolate mofetil; Tac, tacrolimus.
*p ≤ 0.05; **p ≤ 0.001.

malaise, weakness and physical cosmetic symptoms (weight gain, facial changes, oedemas, hair loss) to be more stressful than men. Younger patients were more stressed by physical changes (hair loss, facial changes and gingival hyperplasia) and they reported less trouble with sleep. Less-educated patients more often reported depression, anxiety and stress from leg oedemas and fragile skin. Patients with poor social support were more troubled by diarrhoea. Patients who were on peritoneal dialysis before transplantation reported more trouble with gingival hyperplasia. Stress from facial changes and oedemas was more likely to be present in the first months after transplantation; pain was reported more frequently in later periods.

One of the important medical factors is immunosuppressive medication as it causes adverse effects that are sources of stress for a patient. However, immunosuppressive protocols involve several drugs, so it was impossible to include them in the analysis we performed. For this reason, the analysis of the effect of separate immunosuppressive drugs (steroids, CsA, MMF, Aza, Tac) on each symptom were performed. Surprisingly, the effects were significant only in a few symptoms. When steroid (P) treatment was present, patients reported more stress from facial changes. Patients treated with Aza were more stressed by diarrhoea. Adversely, usage of MMF was connected with less stress from pain, malaise, skin lesions and diarrhoea. There was no relationship between stress and treatment with CsA or Tac.

Table 4. Effects of selected factors on stress from each separate adverse effect of immunosuppression

Symptom	Gender (female)	Age (young)	Education (low)	SoS (low)	Dialysis (peritoneal)	Time (≤ 3)	Type of immunosuppression				
							P	CsA	MMF	Aza	Tac
Pain	↑***	ns	ns	ns	ns	↓*	ns	ns	↓**	ns	ns
Malaise	↑**	ns	ns	ns	ns	ns	ns	ns	↓*	ns	ns
Muscle weakness	↑**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Weight gain	↑**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Facial changes	↑**	↑*	ns	ns	ns	↑**	↑**	ns	ns	ns	ns
Depression	ns	ns	↑*	ns	ns	ns	ns	ns	ns	ns	ns
Fear, anxiety	ns	ns	↑*	ns	ns	ns	ns	ns	ns	ns	ns
Sleep disorders	ns	↓***	ns	ns	ns	ns	ns	ns	ns	ns	ns
Gingival hyperplasia	ns	↑*	ns	ns	↑*	ns	ns	ns	ns	ns	ns
Skin lesions	ns	ns	ns	ns	ns	ns	ns	ns	↓*	ns	ns
Leg oedemas	↑**	ns	↑*	ns	ns	↑*	ns	ns	ns	ns	ns
Hair loss	↑*	↑*	ns	ns	ns	ns	ns	ns	ns	ns	ns
Sexual dysfunction	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Facial oedemas	↑**	ns	ns	ns	ns	↑*	ns	ns	ns	ns	ns
Diarrhoea	ns	ns	ns	↑***	ns	ns	ns	ns	↓*	↑**	ns
Fragile skin	ns	ns	↑**	ns	ns	ns	ns	ns	ns	ns	ns

SoS, satisfaction with social support; dialysis, dialysis modality before transplantation; time, time from transplantation; P, prednison; CsA, cyclosporin A; Aza, azathioprin; MMF, mycofenolate mofetil; Tac, tacrolimus; ns, not significant.
*p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001.
↑(↓) – variable shows increased (decreased) stress in displayed reference category (in parenthesis below main category).

Discussion

This study focuses on non-infectious, non-oncological adverse effects of immunosuppression which patients themselves are able to identify and rate. In contrast to Lough et al., de Geest et al. and Moons et al. (17, 19, 20, 22, 23), we only measured distress and not frequency of adverse symptoms. We found that the most stressful symptoms are pain, weakness, physical changes and psychological symptoms. In general, these results are similar to those from earlier studies (10, 19, 22), but there are some differences from other studies (13, 20), which are possibly caused by predominance of different immunosuppression protocols.

Pain comes at the top of the list of stressors (10, 19, 22). Our patients mostly report backache related to osteoporosis and headache. Stress from pain is gender-specific with females reporting more stress than males (19, 22). As osteoporosis progressively deteriorates with time, pain is reported with increasing frequency as well. Use of MMF enables steroid dose reduction and these patients report less trouble with back pain.

Malaise and muscle weakness are also rated as strong stressors by our patients. A study by Lough et al. with immunosuppression after heart transplantation found a high occurrence of fatigue distress rated as the third item after impotence and overeating (20). Weakness is differently perceived by the two genders. Females are more stressed by these symptoms than males. These results accord with the findings of de Geest et al. (18) and Moons et al. (19). Their female patients ranked stress from muscular weakness in first place in comparison with the males, who ranked it in the fourth place (19, 22, 23). We found a significant reduction of stress from malaise in patients with MMF treatment, probably as a result of lower steroid doses in these patients.

Major cosmetic defects – weight gain and facial changes – are also rated as strong stressors and they disturb significantly more women than men. In addition, distress from facial changes is more often reported in young patients in comparison with the older ones, and in patients in the early post-transplant period compared with those in the late post-transplant period. These differences are connected with steroid use, which are more intensive in early post-transplant period and in young patients (19). Steroid-sparing immunosuppressive regimens, as well as protocols with early withdrawal of steroids, produce fewer side-effects and they improve the patient's well-being (24, 25).

Patients requiring any renal replacement therapies are well-known for their considerable emotional difficulties (10, 12, 13). It is not surprising therefore that we found psychological symptoms (depression, fear, anxiety) strongly represented in our sample. Most papers report that fear of rejection, fear of infection, uncertainty about the future and the possibility of repeated hospitalization are strong sources of anxiety and depression (1–3, 11, 21, 26). Sutton and Murphy found a significant correlation between stressor scores and coping scores (26). Our results suggest that there is some association between education level and psychological symptoms. Higher educated persons seem to develop more coping strategies and so they are less worried and depressed.

The rest of the assessed symptoms show lesser importance. Sleep disorders are more common in older patients, but this pattern is the same in any population. Hair loss and oedemas are uncommon symptoms, and they are felt the same way as major cosmetic defects – they cause stress to more women and younger people. In addition, oedemas are found mostly in the early post-transplant period.

Previous research rated impotence and decreased interest in sex as very stressful for males (12, 13, 19, 20, 22, 23). We were surprised by the low stressfulness of sexual dysfunction among our patients, and we failed to find any gender and age differences. In contrast to our findings, Breza et al. reported a very high prevalence of erectile dysfunction (72%) among transplanted Slovak men in his study (27). We may speculate that sexual troubles are still a taboo amongst the Slovak population, and our study did not intensively focus on this topic, in contrast to the study by Breza et al. (27).

Surprisingly, our study did not identify the type of immunosupressive regimen as a significant factor affecting stress from all adverse effects. Previous research mostly studied protocols based on steroids, CsA and Aza (8, 13, 16, 19, 20, 22, 23). In contrast, the majority of patients in our sample were treated with a combination of CsA, steroids and MMF. Azathioprin was used only in 17.6% of patients. Our findings showed a negative influence of steroids leading to stress from facial changes (e.g. moon face, increased hair growth). This symptom is stressful for patients in the early post-transplant period who are on higher steroid and CsA doses, but after some time, when drugs are tapered down, the importance of this symptom decreases. Today, quick steroid tapering as well as lower CsA levels are allowed due to the use of MMF and antibodies induction therapy (28). This leads to lower occurrence of stress from various

symptoms in mycofenolate-treated patients. As a result, a well-balanced combination of immunosuppressive drugs causes fewer adverse effects and is superior to regimens used in the past. Tacrolimus was recently used only for rescue therapy in Slovakia, so very few patients were recruited into our study. Unfortunately, our Tac subsample is too small (4.6%) to show any significant differences. But in the light of some studies we believe that Tac-based protocols produce better quality of life and fewer adverse effects when compared with CsA (29–31). There is only a limited amount of information about the impact of other new immunosuppressives on patients' life quality. However, it is believed that their use diminishes the side-effects (28).

Our aim was to explore which factors contribute to the severity of stress from adverse effects. The mean total score for stress is relatively low (8.03 of 64) and only gender and education have a significant influence on it. Gender differences unfavourable for females are expected and the female population in general reports more stress and a lower quality of life (17, 19–22). Some previous findings indicate that quality of life after transplantation is negatively related to total stress but positively related to coping (3, 26). We expect people with higher education to use more efficient coping strategies, which decrease their stress. However, this statement needs further evaluation.

From the patient's perspective the most stressful non-infectious non-oncological adverse effects of immunosuppression are pain, weakness, cosmetic changes and psychological symptoms. The stress from adverse effects is higher in women and less-educated patients. The type of immunosuppressive regimen does not seem to influence the overall score of stress, but the use of new drugs exhibits less stress in some symptoms. More research should be performed in this field to identify the best-balanced protocols with minimum of adverse effects. Such efforts can identify patients at risk of severe adverse effects. This could help to decrease their stress and thus improve quality of life for kidney transplant recipients. Diminished stress from adverse effects can contribute to reduction of their non-compliance and thus can help to prevent graft damage because of late acute rejection episodes, which will lead to prolonged graft and patient survival.

Acknowledgements

This work was supported by Science and Technology Assistance Agency under the contract No. APVT-20-028802.

References

1. Hayward MB, Kish JP, Frey GM, Kirchner JM, Carr LS, Wolfe CM. An instrument to identify stressors in renal transplant recipients. ANNA J 1989: 16: 81.
2. Frey GM. Stressors in renal transplant recipients at six weeks after transplant. ANNA J 1990: 17: 443, 450.
3. White MJ, Ketefian S, Starr AJ, Voepel-Lewis T. Stress, coping, and quality of life in adult kidney transplant recipients. ANNA J 1990: 17: 421, 431.
4. El Agroudy AE, Bakr MA, El Dein ABS, Ghoneim MA. Death with functioning graft in living donor kidney transplantation: analysis of risk factors. Am J Nephrol 2003: 23: 186.
5. Ducloux D, Motte G, Billerey C et al. Cyclosporin withdrawal with concomitant conversion from azathioprine to mycophenolate mofetil in renal transplant recipients with chronic allograft nephropathy: a 2-year follow-up. Transplant Int 2002: 15: 387.
6. Penn I. Occurrence of cancers in immunosuppressed organ transplant recipients. Clin Transplant 1998: 12: 147.
7. Newstead CG. Assessment of risk of cancer after renal transplantation. Lancet 1998: 351: 610.
8. Hetzer R, Albert W, Hummel M et al. Status of patients presently living 9 to 13 years after orthotopic heart transplantation. Ann Thorac Surg 1997: 64: 1661.
9. Aker S, Ivens K, Guon Z, Brabensee B, Heering P. Cardiovascular complications after renal transplantation. Transplant Proc 1998: 30: 2039.
10. Laupacis A, Pus N, Muirhead N, Wong C, Ferguson B, Keown P. Disease-specific questionnaire for patients with a renal transplant. Nephron 1993: 64: 226.
11. Fallon M, Gould D, Wainwright SP. Stress and quality of life in the renal transplant patient: a preliminary investigation. J Adv Nurs 1997: 25: 562.
12. Hricik DE, Halbert RJ, Barr ML et al. Life satisfaction in renal transplant recipients: preliminary results from the transplant learning center. AJKD 2001: 38: 580.
13. Matas AJ, Halbert RJ, Barr ML et al. Life satisfaction and adverse effects in renal transplant recipients: a longitudinal analysis. Clin Transplant 2002: 16: 113.
14. Jindal RM, Baines LS. Noncompliance after solid organ transplantation. Transplantation 2001: 72: 1583.
15. Hathaway DK, Combs C, de Geest S, Stergachis A, Moore LW. Patient compliance in transplantation: a report on the perceptions of transplant clinicians. Transplant Proc 1999: 31(Suppl. 4A): 10S.
16. Baines LS, Joseph JT, Jindal RM. Compliance and late acute rejection after kidney transplantation: a psychomedical perspective. Clin Transplant 2002: 16: 69.
17. de Geest S, Borgermans L, Gemoets H et al. Incidence, determinants, and consequences of subclinical noncompliance with immunosuppressive therapy in renal transplant recipients. Transplantation 1995: 59: 340.
18. de Geest S, Abraham I, Dunbar-Jacob J. Measuring transplant patients' compliance with immunosuppressive therapy. West J Nurs Res 1996: 18: 595.
19. Moons P, de Geest S, Abraham I, van Cleemput J, Vanhaecke J. Symptom experience associated with maintenance immunosuppression after heart transplantation: patients' appraisal of side effects. Heart Lung 1998: 27: 315.
20. Lough ME, Lindsey AM, Shinn JA, Stotts NA. Impact of symptom frequency and symptom distress on self-reported quality of life in heart transplant recipients. Heart Lung 1987: 16: 193.

21. Valderrábano F, Jofre R, López-Gómez JM. Quality of life in end-stage renal disease patients. AJKD 2001: 38: 443.
22. Moons P, Fairchild S, de Geest S. Patients' appraisal of side effects in quality of life assessments of immunosuppressive regimens. In: Cochat P, Traeger J, Merieux C, Derchavane M, eds. Immunosuppression under Trial. Dordrecht: Kluwer Academic Publishers, 1999: 69.
23. de Geest S, Moons P. The patient's appraisal of side-effects: the blind spot in quality-of-life assessments in transplant recipients. Nephrol Dial Transplant 2000: 15: 457.
24. Hasselder A. Renal transplant: long-term effects of immunosuppression. Prof Nurse 1999: 14: 771.
25. Jensen S, Jackson EC, Riley L, Reddy S, Goebel J. Tacrolimus-based immunosuppression with steroid withdrawal in pediatric kidney transplantation – 4-year experience at a moderate-volume center. Pediatr Transplant 2003: 7: 119.
26. Sutton TD, Murphy SP. Stressors and patterns of coping in renal transplant patients. Nurs Res 1989: 38: 46.
27. Breza J, Reznicek J, Pribylincova V, Zvara P. Erectile dysfunctions in patients treated with hemodialysis and kidney transplantation. Bratisl Lek Listy 1993: 94: 489.
28. Keown P. Improving quality of life – the new target for transplantation. Transplantation 2001: 72(Suppl.): SS67.
29. Reimer J, Franke GH, Philipp T, Heemann U. Quality of life in kidney recipients: comparison of tacrolimus and cyclosporine-microemulsion. Clin Transplant 2002: 16: 48.
30. Reimer J, Franke GH, Kohnle M, Philipp T, Heemann U. Quality of life after kidney transplantation – the impact of tacrolimus. Transplant Proc 2001: 33: 1924.
31. Shield CF III, McGrath MM, Goss TF. Assessment of health-related quality of life in kidney transplant patients receiving tacrolimus (FK506)-based versus cyclosporine-based immunosuppression. Transplantation 1997: 64: 1738.